

IRB # 2016- 6966

Title: A program of enhanced recovery after cesarean birth to improve postoperative recovery and reduce hospital length of stay

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Background: Enhanced recovery after surgery (ERAS) involves changes to multiple aspects of perioperative care with the aim of standardizing postoperative patient care, improving patient outcomes, reducing postoperative length of stay, and optimizing patient satisfaction. Enhanced recovery pathways have been widely implemented in many different areas of surgery. Initially, these pathways were introduced in colorectal surgery nearly 15 years ago, but have found more widespread usage in specialties including urology, orthopedics, breast surgery and gynecologic surgery. Initiation of enhanced recovery programs have consistently resulted in reduced hospital length of stay, financial savings and improved patient satisfaction.¹

To date, only one observational study in obstetrics has been performed looking at the introduction of an enhanced recovery pathway in the United Kingdom. In that study the investigators were able to successfully introduce an enhanced recovery program to their obstetrics unit and noted a greater proportion of patients discharged earlier with improved patient satisfaction, without a concomitant increase in readmission rates.²

The components of enhanced recovery pathways vary significantly, though all seek to provide benefit to the patient by optimizing the postoperative recovery course through the combination of multiple evidence-based practices. In previous studies aimed at post-cesarean birth discharge timing, comparing early versus usual discharge time, there was no difference observed in the number of maternal readmissions, maternal antibiotic use, maternal well-being and anxiety or depression.³

Components of enhanced recovery pathways can include standardizing the use of prophylactic antibiotics, venous thromboembolism prophylaxis, minimizing starvation times, use of antiemetics, earlier resumption of feeding postoperatively, use of chewing gum postoperatively, early removal of dressings and urinary catheters, and standing postoperative pain medication orders. Prophylactic antibiotics and venous thromboembolism prophylaxis are routinely recommended at the time of cesarean deliveries by the American Congress of Obstetricians and Gynecologists.⁴⁻⁵ In addition, the American Society of Anesthesiologists recommends minimizing preoperative starvation times with moderate amounts of clear liquids up to 2 hours prior to induction of anesthesia and solid foods up to 6-8 hours preoperatively.⁶ Routine administration of antiemetics at the time of cesarean to reduce early postoperative nausea and vomiting may allow earlier resumption of feeding after cesarean.⁷ Several studies have determined that early resumption of feeding after cesarean resulted in early ambulation, greater maternal satisfaction, and reduced length of hospital stay, with no detrimental outcomes.⁸⁻¹² Moreover, the introduction of chewing gum postoperatively has resulted in a reduction in postoperative ileus after cesarean.¹³⁻¹⁵

A recent randomized controlled trial evaluating the early removal of wound dressings at 6 hours postoperatively, noted there was no detrimental effect on incision healing with early removal permitting earlier attention to personal hygiene with greater patient satisfaction.¹⁶ Additionally, a randomized controlled trial of Ketorolac use at cesarean birth resulted in reduced postoperative pain and narcotic use.¹⁷ Early removal of urinary catheters postoperatively were also associated with a lower risk of infection and earlier postoperative ambulation.¹⁸

Currently, no randomized studies exist in the literature specifically addressing the potential impact of an enhanced recovery pathway in among women undergoing cesarean births on postoperative outcomes and postoperative length of stay in the United States. We aim to implement an enhanced recovery pathway at the time of cesarean birth to expedite the postoperative recovery process, thereby reducing postoperative hospital length of stay.

Hypothesis: We hypothesize that an enhanced recovery program at the time of cesarean birth in obstetrics will promote early ambulation, resumption of diet and initiation of breastfeeding, and reduce postoperative hospital length of stay.

Currently, patients are encouraged to ambulate on the first post-operative day, but it is largely left up to the patient when to actually begin to ambulate. They are similarly offered a diet on the first postoperative day but are not encouraged to eat. Breastfeeding is more systematically encouraged early as part of Montefiore's effort to get baby friendly designation. And finally, patients are typically discharged on postoperative day number three unless complications arise in the newborn or the mother.

As part of this study, patients in both the enhanced recovery and usual care group will be offered the opportunity to be discharged from the hospital on postoperative day number 2 if their recovery is going well and if they choose not to leave then, they will be encouraged to return home on postoperative day number 3 according to the current standard of care.

Null hypothesis: An enhanced recovery program at the time of cesarean birth will have no impact on postoperative hospital length of stay (our primary outcome variable).

Objective: To determine whether women randomized to an enhanced recovery program will have improved postoperative outcomes, improved breastfeeding initiation and continuation, reduction in hospital length of stay without compromising patient satisfaction in comparison to standard of care postoperative recovery interventions.

Materials and Methods: This will be a prospective non-blinded randomized controlled study of women presenting for care to the Montefiore Medical Center. All patients will undergo routine obstetrical care and preparation for cesarean birth as if they were not participating in the research study. Women participating in the study will be greater than 37 0/7 weeks gestation based on their estimated due date calculated from last menstrual period or early ultrasound. The women participating in the study will be undergoing either: 1. Scheduled cesarean birth or 2. Non-emergent cesarean birth. Non-emergent cesarean birth will be defined as an indicated cesarean birth based on obstetrical criteria without significant fetal heart tracing abnormalities. This would include women diagnosed with a labor dystocia or arrest of labor, failed labor induction, fetal malpresentation in labor (i.e. breech presentation) or any other non-emergent indication for cesarean birth in which there is no immediate danger to mother or fetus. Patient consent will occur on admission to the obstetrical labor and delivery unit for elective cesarean births. Because patients presenting to our units may be in pain and pain may compromise cognition and judgment, at the time of actual enrollment, the principal investigator or his or her designee will assess the capacity of the patient to provide ethically and legally adequate informed consent and will document that finding in the research record. If at the time they are approached for actual involvement in the protocol, they are in too much pain to have the informed consent discussion and provide consent, they will not be considered for participation. Women that accept participation will be randomly assigned to an enhanced recovery program or routine perioperative care. Using a random sequence number table, we will generate block randomization. Allocations will be placed in sequentially numbered opaque sealed envelopes.

Postoperative recovery will follow the usual service protocols as if the patient were not in the study with the exception of components of the enhanced recovery protocol, which will include several evidence based recommendations (see Enhanced Recovery Protocol components, below) including early ambulation, early diet initiation, early removal of urinary catheter, early removal of postoperative dressing and standing ketorolac for 24 hours postoperatively.

Maternal demographics to be obtained will include body mass index (BMI), gestational age, pre-operative and post-operative day #1 complete blood count, estimated blood loss, surgical time from skin incision to closure, skin closure method, birth weight, Apgar scores, newborn outcomes, indication for cesarean birth, medical history and any antenatal complications, past surgical history, postoperative course and intra-operative and post-operative complications.

All patients will be followed until the routine postpartum visit occurs at 6-8 weeks following cesarean birth. Postpartum visit information will be extracted from the medical record. The

patient will then be contacted by telephone at 8 weeks after cesarean birth and asked about her postoperative course regarding her overall satisfaction with her postoperative care and if any postoperative complications arose during the postpartum period.

A description of this clinical trial is available on www.ClinicalTrials.gov, as required by U.S. law. The clinicaltrials.gov identifier for the study is NCT02956616.

Enhanced Recovery Protocol Components:

1. Provide preoperative education about the perioperative recovery experience including postoperative analgesia, thromboprophylaxis and breastfeeding education - Patients will be provided with standardized printed instructions for the perioperative experience
2. Minimize preoperative starvation times
 - a. Moderate amount of clears up to 2 hours prior to anesthesia - patients will be encouraged to consume a moderate amount of clear liquid diet up to 2 hours prior to anesthesia.
 - b. Solid foods up to 6-8 hours prior to anesthesia - solid foods will be encouraged up to 6-8 hours preoperatively, in contrast to the current practice of all patients limiting food intake after midnight the day of surgery.
3. Prophylactic antibiotics - currently offered as the standard of care to all patients undergoing cesarean birth, based on recommendations from the American Congress of Obstetricians and Gynecologists
4. Venous thromboembolism prophylaxis (mechanical) initiated at the time of cesarean birth and continued postoperatively - currently offered as the standard of care at our institution with sequential compression devices at the time of cesarean birth and immediately postoperatively with provision of chemoprophylaxis with subcutaneous heparin after 24 hours from the time of the procedure
5. Chewing gum (Xylitol) to reduce postoperative ileus - Xylitol chewing gum will be provided to patients immediately after the procedure and will be provided 3 times per day for a duration of 30 minutes at each time, based on a metanalysis and systematic review. Patient's will be encouraged on its use for return of bowel function.
6. Routine administration of Non-steroidal anti-inflammatory drug, Ketorolac (toradol), Intravenous 15mg every 6 hours for 24 hours postoperatively to minimize postoperative narcotic use. First dose will be provided 6 hours after procedure with 3 subsequent doses every 6 hours for a total of 4 doses over 24 hours.
7. Early initiation of feeding after cesarean, immediately for clears, 30 minutes for regular diet as tolerated - This is in contrast to the current practice of limiting postoperative feeding until a minimum of 2 hours after cesarean birth once the patient has left the PACU
8. Early removal of urinary catheter (12 hours postoperatively) - An order will be placed at the completion of the procedure to discontinue the urinary catheter 12 hours postoperatively
9. Early removal of dressing (6 hours postoperatively) - An order will be placed at the completion of the procedure to instruct removal of the postoperative dressing at 6 hours postoperatively

10. Early mobilization at 12 hours after cesarean birth - An order will be placed at the completion of the procedure to encourage patients to begin ambulating 12 hours after the cesarean birth
11. Early skin-to-skin/breastfeeding initiation - this is the standard of care at our institution in which skin-to-skin contact and breastfeeding are initiated as soon as possible in the operating room or PACU
12. Early incentive spirometry - An order will be placed at the completion of the procedure to provide an incentive spirometer and patients will be encouraged immediately following the surgical procedure in the postoperative anesthesia care unit

Routine Recovery Protocol Components (control group):

1. Oral intake prior to procedure – patients will be required to limit food intake to at least 8 hours prior to the cesarean birth or after midnight the day of the procedure as is current standard of practice
2. Prophylactic antibiotics - currently offered as the standard of care to all patients undergoing cesarean birth, based on recommendations from the American Congress of Obstetricians and Gynecologists
3. Venous thromboembolism prophylaxis (mechanical) initiated at the time of cesarean birth and continued postoperatively - currently offered as the standard of care at our institution with sequential compression devices at the time of cesarean birth and immediately postoperatively with provision of chemoprophylaxis with subcutaneous heparin after 24 hours from the time of the procedure
4. Patients will be provided with routine regional anesthetic per current anesthesia protocol
5. Patients are currently offered non-steroidal anti-inflammatory (Ibuprofen) and Percocet on an as needed basis for pain control postoperatively
6. Patients will be provided with a meal as early as 2 hours postoperatively once the patient has been transferred from the postoperative anesthesia care unit
7. Urinary catheter will be removed on postoperative day #1 as is the current standard of practice in our institution
8. Wound dressings will be removed on postoperative day #1 as is the current standard of practice in our institution
9. Patients will mobilize once sensation and motor function of the lower extremities returns
10. Early skin-to-skin/breastfeeding initiation - this is the standard of care at our institution in which skin-to-skin contact and breastfeeding are initiated as soon as possible in the operating room or PACU
11. Patients will be provided with an incentive spirometer once they arrive on the postpartum unit which is the current standard of practice in our institution.
12. Control group participants may receive IV ketorolac for pain control

Primary Outcome:

1. Postoperative length of hospital stay

Secondary Outcomes:

1. Postoperative pain medication requirements
2. Breastfeeding initiation and continuation rates
3. Patient satisfaction
4. Maternal-neonatal bonding
5. Time to ambulation
6. Time to resumption of normal activity
7. Time to attempting oral feeding
8. Total length of hospital stay
9. Postoperative infections from expedited removal of catheter versus removal of wound dressing
10. Readmission rates
11. Postpartum depression/anxiety

Inclusion criteria:

1. Women undergoing a non-urgent or elective cesarean birth >37 weeks gestation

Exclusion criteria:

1. Women undergoing an urgent or emergent cesarean birth
2. Women less than 18 years old
3. Patients receiving general anesthesia
4. Abnormally adherent placenta (Placenta Accreta) or expected excessive blood loss (Placenta accrete)
5. Pre-existing essential hypertension or hypertensive disorders of pregnancy (preeclampsia, eclampsia, HELLP)
6. Chronic or acute renal impairment
7. Bleeding disorders or platelet dysfunction
8. Peptic ulcer disease or gastrointestinal bleeding
9. Known hypersensitivity to ketorolac (toradol)
10. Active infection at the time of cesarean
11. Cesarean birth prior to 37 weeks
12. Women in significant pain in labor

Sites: Montefiore Medical Center (Both Weiler and Wakefield on their labor floors)

Study size and Power: Patients are routinely discharged on postoperative day number 3 or approximately 72 hours postoperatively at Montefiore Medical Center following cesarean birth. Our primary outcome variable will be postoperative length of hospital stay. Patients in the routine perioperative care group and the enhanced recovery protocol group will be offered the opportunity to be discharged on postoperative day number 2 or approximately 48 hours postoperatively at the discretion of the obstetric attending physician. Our experience is that no more than 10% of patients are discharged home on postoperative day number 2 or approximately 48 hours postoperatively. We therefore have calculated that if we anticipate an increase in the rate of early discharges on postoperative day number 2 from 10% to 30% with

the enhanced recovery pathway will require 59 subjects in each group, and 118 total participants, with an alpha error of 0.05 and a power of 80%. Patients in the control group will continue to be offered Ketorolac for postoperative analgesia which is considered standard of care in our institution. Approximately 65 percent of patients after cesarean deliveries from a recent chart review receive ketorolac of at least one dose. Given that our primary outcome measure is postoperative length of stay, and patients receiving ketorolac at present still routinely are discharged on postoperative day number 3, we do not anticipate that this will produce a contamination factor with respect to our primary outcome measure which is postoperative length of stay. As a result, our power calculation would therefore still remain valid for our primary outcome measure.

Risks/Benefits:

Ketorolac tromethamine, including Toradol can cause peptic ulcers, gastrointestinal bleeding and/or perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Ketorolac is contraindicated in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding. NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk Ketorolac is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft surgery. Ketorolac is contraindicated in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion. Toradol inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding

Limited data from one published study involving 10 breastfeeding women 2-6 days postpartum showed low levels of ketorolac in breast milk. Levels were undetectable (less than 5 ng/mL) in 4 of the patients. After a single administration of 10 mg of Ketorolac, the maximum milk concentration observed was 7.3 ng/mL, and the maximum milk-to-plasma ratio was 0.037. After 1 day of dosing (10 mg every 6 hours), the maximum milk concentration was 7.9 ng/mL, and the maximum milk-to-plasma ratio was 0.025. Assuming a daily intake of 400-1,000 mL of human milk per day and a maternal body weight of 60 kg, the calculated maximum daily infant exposure was 0.00263 mg/kg/day, which is 0.4% of the maternal weight-adjusted dose. Exercise caution when ketorolac is administered to a nursing woman. Available information has not shown any specific adverse events in nursing infants; however, instruct patients to contact their infant's health care provider if they note any adverse events. The American academy of pediatrics has found ketorolac to be compatible with breastfeeding.

There are no known risks to this study beyond that of routine postoperative care at the time of cesarean birth in addition to the aforementioned use of Ketorolac. All patient information will be kept confidential. Patient research records will be kept confidential and names will not be used in any written or verbal reports. The patient's information will be given a code number and separated from your name or any other information that could identify them. All information will be kept in a secure manner and computer records will be password protected. Study information will be kept as long as they are useful for the completion of the research study after which they will be destroyed.

The patient will not experience any direct benefit personally from participation in this study. The benefit of participation in this study will generate important information about improving postoperative recovery at cesarean birth.

Data Management: Data collected in this study protocol will be extracted from the secure password protected computer programs utilized by Montefiore for patient care: Epic / ASOBGYN/ EPFweb. Information extracted for study use will be maintained on a password protected computer in a locked office and not accessible to others. Once the clinical information obtained on a patient is completed the information will be de-identified. Patient confidentiality will be maintained at all times.

Statistics: To achieve comparable groups we will randomize enrollees to one of two treatment arms. Randomization will be done with block sizes of 4 to reduce the likelihood of unmasking the randomized assignment. Randomization will be done according to separate lists generated through www.randomization.com. Randomization will be performed by Dr. Catherine Igel. No patient identifying information will be entered into this website as this will be done prior to enrollment in the study

The primary aim of the study is to compare whether women randomized to an enhanced recovery program will have improved postoperative outcomes, breastfeeding initiation, reduction in length of stay without compromising patient satisfaction in comparison to standard of care postoperative recovery interventions. The primary analysis will be a chi-square comparison of proportions of the 2 x 2 table of study arm (experimental/control) and hospital length of stay (shortened length of stay/standard length of stay). We will also assess an odds ratio (with 95% confidence interval) for additional outcome measures: Postoperative pain medication requirements, Breastfeeding initiation and continuation rates and patient satisfaction will be determined by a follow-up survey performed greater than 4 weeks postoperatively.

Data safety monitoring Plan (DSMP): In order to maintain additional patient safety, a DSMP will be in place for the study. The data will be reviewed by two clinicians familiar with cesarean birth and perioperative and postoperative management and complications who are not part of the study, namely Dr. Rodney Wright and Dr. Ashlesha Dayal. In addition, a statistician who is not part of the study will review the data, Dr. Shankar Viswanathan. The Data safety monitoring committee will meet every 6 months. Minutes of the meetings including attendance, a summary of discussion and any relevant findings will be recorded. Data will be reviewed for adverse events throughout the study duration. The results of findings and recommendations of the team will be reported to the Albert Einstein College of Medicine institutional review board for review and action.

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